REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Claims 2 and 8 have been amended to remove non-elected subject matter that was inadvertently not omitted in the Preliminary Amendment filed with the applicant's election. Claim 12 has been amended in a manner which is believed to clarify the meaning of this claim, as will be further discussed below. Following entry of the above amendments, claims 1-3, 5-6 and 8-10 and 12 are pending in this application.

Specification Amendments

An Abstract has been provided, typed on a separate page as requested by the Examiner. However, it should be recognized that this is a duplicate of the Abstract properly filed in the international application, and included with this application as filed. The purpose of this duplicate Abstract is therefore not understood. The Examiner's attention is respectfully called to MPEP ¶1893.03(e), which provides in part:

> Since applicant has already complied with PCT Rule 11.4 by filing the abstract on a separate sheet when the international application was filed, it is improper for the examiner of the U.S. national stage application to require an abstract on a separate sheet during national stage processing of the international application.

The title has also been amended in the manner suggested by the Examiner.

Claim Rejections – 35 USC § 112 – "in-vivo cleavable ester"

Claims 1-3, 5, 6, 9, 10 and 12 have been rejected with respect to the term "*in-vivo* cleavable ester" under section 112, second paragraph, as being indefinite (Action pages 2-3) and under section 112, first paragraph, as being subject matter "not described in the specification" Action pages 4-5, for a variety of reasons. These reasons are set out in numbered points below in order to facilitate further discussion:

1. "Applicants' "*in-vivo* cleavable ester" are molecules whose structure lie outside the subject matter of claim 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of claim 1." (Action pages 3).
2. "The claim describes the function intended but provides no specific structural guidance to what constitutes an "*in-vivo* cleavable ester". . . . Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise." (Action page 3).
3. "Nowhere in the specification are directions given for preparing any '*in-vivo* cleavable ester' of the claimed compounds. Since the structures of these '*in-vivo* cleavable ester", compounds are uncertain, direction for their preparation must be even more unclear." (Action page 5).
4. "In addition, determining if a particular substance is a '*in-vivo* cleavable ester' will involve undue experimentation. How much cleavage is required and how fast must it be? Must the cleavage occur only in humans or may it occur in any organism?"

The basis for these statements is not understood, when one considers the specification disclosure and the extensive use of the terms, concept and structure of *in-vivo* cleavable (or hydrolysable) esters and "pro-drugs" throughout the pharmaceutical literature and patents (including patent claims). These grounds for rejection, therefore, are respectfully traversed.

First of all, there is direct specification support *and written description* for "*in-vivo* cleavable esters" as a type of pro-drug at page 22, line 24 through page 23, line 13. This disclosure reads, in part:

> Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:
>
> a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
>
> b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
>
> c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
>
> d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
>
> e) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984).
>
> **Examples of such pro-drugs may be used to form in-vivo-cleavable esters of a compound of the Formula I. An in-vivo-cleavable ester of a compound of the Formula I containing a carboxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include** (1-6C)alkoxymethyl esters, for example methoxymethyl; (1-6C)alkanoyloxymethyl esters, for example pivaloyloxymethyl; phthalidyl esters; (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters, for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters, for example 5-methyl-1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters, for example 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention.

(Emphasis added).

The specification thus cites five literature references that were available to the art at the time the present invention was made, which detail the concept and design of prodrugs, including prodrugs in ester form. Moreover, a recent search of the U.S. PTO patent database

for patents granted in the years 1996-2002 identified 866 patents in which one or more claims include the term "prodrug," and the same search of patents granted in the years 1991-1995 identified 127 patents having such claims.

It is respectfully submitted that this multitude of patents with claims including "prodrugs" makes clear that the meaning and structure of prodrugs is and was well understood, including prodrugs in an ester form. Most of these patents include significantly less guidance than the present specification but, on the other hand, make clear that persons skilled in the art will have no difficulty in understanding and practicing the preparation and use of prodrugs, such as presently claimed. Some of these references, like the present specification, refer the reader to literature references for more details if needed. Excerpts from a few of the many patents including specific reference to hydrolysable or cleavable esters as prodrugs, are as follows:

U.S. Patent 6,465,467 (issued October 15, 2002)

> The term "prodrug forms" means a pharmacologically acceptable derivative, at such as an ester or an amide, which derivative is biotransformed in the body to form the active drug. Reference is made to Goodman and Gilman's, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15. (Col. 8, lines 21-26).

U.S. Patent 5,726,182 (issued March 10, 1998)

> The term "prodrug", as of the compounds of formula I, refers to derivative compounds that are rapidly transformed in vivo to yield the parent compound of the formula I, as for example by hydrolysis in blood. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975). Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E. B. Roche, Pergamon Press: New

York (1987). It is intended that these references, and any others cited throughout this specification, are incorporated herein by reference.

The term "prodrug ester group" refers to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art, including a (5-R-2-oxo-1,3-dioxolen-4-yl)methyl group. Other examples of prodrug ester groups can be found in the book "Pro-drugs as Novel Delivery Systems", by Higuchi and Stella, cited above. (Col. 21, lines 10-31).

U.S. Patent 5,616,591 (issued April 1, 1997)

It should be understood that the present invention includes prodrug forms, such as ester, acetal and/or mixed acetal derivatives of the compounds of formula I. For example, such derivatives have been documented in Design of Prodrugs, edited by H. Bundgard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder et al. (Academic Press, 1985). Further, it is understood that any moiety at R_6 and/or R_7 that will be cleaved in vivo to provide an acidic R_6 and/or R_7 moiety is within the spirit and scope of this invention. (Col. 3, lines 57-67)

U.S. Patent 5,468,757 (issued November 21, 1995)

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically clearable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. (Col. 7, line 62 through col. 8, line 14)

Thus, in addition to the disclosure in the present specification at pages 22-23, the pharmaceutical art is replete with guidance (both in literature and issued patents) on making prodrugs of pharmaceutical compounds, including in ester form which would be "*in vivo* cleavable."

The specific points raised by the Examiner (as numbered above) can each be answered and overcome by consideration of the present specification disclosure, and what was clearly known in the art as evidenced by the above patents and literature references:

In point 1, the Examiner asserts that an "*in-vivo* cleavable ester" is a molecule whose structure lies outside the subject matter of claim 1, but is converted by the body's metabolism to active compounds falling within the structural scope of claim 1. To the contrary, the compounds of the present invention are stated throughout the specification and in the claims to specifically include "*in-vivo* cleavable esters." It is respectfully submitted that persons skilled in this art, drawing upon the knowledge of the art as exemplified by the cited literature, and particularly having the guidance provided in the specification, would have no difficult understanding the scope and structure of the claimed compounds, including their structure in "*in-vivo* cleavable ester" form.

In point 2, the Examiner asserts that the claim "describes the function intended but provides no specific structural guidance to what constitutes an '*in-vivo* cleavable ester.'" To the contrary, it should now be clear from the above discussion that such "specific structural guidance" is given both in the specification and in the literature known and available to persons skilled in this art.

In point 3, the Examiner asserts that "nowhere in the specification are directions given for preparing any '*in-vivo* cleavable ester' of the claimed compounds. To the contrary, the specification at pages 22-23 recites a number of reactants that can be used to form the "*in-vivo* cleavable esters" as claimed, and many other reactants for forming such prodrug esters are exemplified in the cited literature. Clearly, a skilled pharmaceutical chemist would

know how to make an ester from these reactants, or would know how to find suitable reaction schemes in the available literature.

Finally, as quoted in numbered point four above, the Examiner asserts that "determining if a particular substance is a '*in-vivo* cleavable ester' will involve undue experimentation. How much cleavage is required and how fast must it be? Must the cleavage occur only in humans or may it occur in any organism?" Again, it should be clear from the above discussion that the relevant concepts and structures were so well known and reported in the patent and published literature that persons skilled in the art would have had no problem understanding and practicing the invention as claimed. The Federal Circuit has repeatedly made clear that the emphasis is on "undue", not whether some experimentation may be required. See, for example, *PPG Industries Inc. v. Guardian Industries Corp.* 37 USPQ2d 1618, 1623 (Fed. Cir. 1996):

> Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made, based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:
>
> > The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.
>
> *Ex parte Jackson*, 217 USPQ 804, 807 (1982).

Considering the extensive knowledge in the art at the time of the present invention pertaining to prodrugs in general and *in-vivo* cleavable or hydrolysable esters, in particular, and the guidance provided by the present specification, any experimentation that might have been required to practice this embodiment of the present invention would have been, at worst, a routine matter.

Therefore, it is submitted that the term "*in vivo* cleavable ester" in context of this invention would have been clearly understood by persons skilled in this art, and such persons would have been able to practice this embodiment of the invention without undue experimentation at the time the application for this invention was filed. Accordingly, it is respectfully requested that these section 112 grounds for rejection be withdrawn.

Claim Rejections – 35 USC § 112 – Method Claim 12

Method claim 12 has been rejected under section 112, second paragraph as being indefinite, in that (1) it "does not set forth any steps involved in determining what is 'a disease or medical condition mediated by a cytokine'" and (2) that it is unclear what diseases and treatments applicant is intending to encompass. The Examiner continues, "identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research" and that "with out such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claims."

The Examiner has also rejected claim 12 under section 112, first paragraph, as not being enabled. The Examiner acknowledges that the specification is enabling for the

treatment of rheumatoid arthritis and psoriasis, but asserts that it "does not reasonably provide enablement for every 'disease or medical condition mediated by a cytokine'."

These grounds for rejection are respectfully traversed, since this very type of claim is expressly authorized in the US PTO Utility Guidelines in a context that is no more definite or enabling than the present specification disclosure.

Claim 12, as amended above, now provides:

> 12. (Amended) A method for treating a disease or medical condition mediated by the production or effect of a cytokine, said method comprising administering to a warm-blooded animal in need thereof a cytokine inhibiting amount of an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in-vivo cleavable ester thereof, according to claim 1.

It is well established that there is no need to recite specific disease or medical conditions in a claim in the form of claim 12, provided persons skilled in the art are aware of at least one condition which may be treatable by the claimed method. Moreover, there is no requirement that the specification or claim identify each and every disease or medical condition that can be treated by the claimed method, as the Examiner is apparently now requireing.

In this regard, the Examiner's attention is respectfully called to the current Revised Interim Utility Guidelines and Training Materials available, *inter alia*, on the PTO website. In particular, Example 8 of the Utility Guidelines: Training Examples, entitled "'Therapeutics' Not Associated with a Disease" authorizes claims very similar to present claim 12. A copy of releavnt portions of the Training Examples is attached for the Examiner's convenience, specifically pages 1-2 and 45-49. As will be explained further below, even though these Utility Guidelines are focused on the utility requirements of sections 101 and 112, second paragraph, they necessarily are also relevant to the present

section 112 grounds for rejection, which have been characterized as being based on indefiniteness and lack of enablement.

At page 45 of the Training Materials, Example 8 is set out for analysis. The assumed specification content and claim wording used for the analysis are as follows::

> **Specification:** Compound A is disclosed to inhibit enzyme XYZ, a well-inown enzyme which is a member of the family of tyrosine kinase, *in vitro*. The specification states that compound A can be used to treat diseases carused or exacerbated by increased activity of enzyme XYZ. No actual diseases are named.
>
> **Claims:**
>
> 1. Compound A.
>
> 2. A method of treating a disease caused or exacerbated by increased activity of enzyme XYZ consisting of administering an effective amount of compound A to a patient.

Although the Training Materials focus on utility, the "analysis" makes clear that both claims 1 and 2 are of an acceptable format and content *in all respects*, provided that at least one disease condition is identified in the specification or known in the art that can is treatable by the method.

The Training Materials initially assume that that "no actual diseases are named" in the specification. Since claim 2 is directed to a method of using the compound of claim 1, the analysis first considered the utility of claim 1. The analysis notes that XYZ is a well-known tyroxine kinase enzyme, and the substrate for the enzyme and the reaction which the enzyme catalyzes are also well known. Since the specification discloses that compound A will inhibit enzyme XYZ *in vitro*, claim 1 was found to meet the utility requirements, even though no no

actual diseases treatable by the inhibition of enzyme XYZ are named in the specification. (Training Materials page 45).

However, method claim 2 was *initially* found to be rejectable under section 101 and section 112, first paragraph. As discussed in paragraph 4) at pages 46-47 of the Training Materials, since neither the specification nor the art of record disclose any diseases or conditions caused or exacerbated by enzyme XYZ, the asserted utility essentially is a method of treating an unspecified, undisclosed disease or condition, which does not define a "real world" context of use. The paragraph continues, "treating an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a 'a real world' context of use." In these assumptions it is concluded at the top of page 47 that claim 2 should be rejected under both section 101 and section 112, first paragraph.

However, the Training Materials at page 47 then proceed to itemize situations under which the rejections should be withdrawn. In the first situation set out in paragraph (1), the examiner is instructed to withdraw the rejections of claim 2 under section 101 and 112, first paragraph, if applicant provides a reference published before the filing date of the application which teaches that certain diesease are associated with increased activity of enzyme XYZ.

If an applicant can overcome the rejections by citing a published reference identifying a specific disease, then it is clear that the rejection never would have arisen in the first place if at least one such specific disease condition had been identified in the specification. There is no requirement that this specific disease condition be set forth in the claim. Moreover, there clearly is no requirement that every disease condition that is treatable by the method of claim 2 be set forth in the claim itself, or even identified in the specification.

It is acknowledged that this Example 8 in the Training Materials most directly concerns lack of utility rejections under sections 101 and 112, second paragraph. However, it would be rather disingenuous of the Patent Office to exemplify a specific method claim format and circumstance as meeting all utility requirements, if that very claim format and circumstance *could not possibly* also meet other claim requirements, such as enablement and definiteness. But that would be the situation if the present rejections of claim 12 are maintained. The Examiner's grounds for rejection of claim 12 are therefore inconsistent with the Guidelines and Training Materials promulgated by the Patent Office itself, and thus should be withdrawn.

First of all, the Examiner acknowledges that the specification is enabling with respect to the treatment of *at least one* specific disease conditions, specifically rheumatoid arthritis and psoriasis. Thus, the focal point of Example 8 of the Training Materials is met by the present specification and claims, and there can be no question but that all aspects of the utility requirements of sections 101 and 112, first paragraph, are met by present claim 12. However, in supporting his section 112, first and second paragraph rejections of claim 12, the Examiner observes that this disclosure "does not reasonably provide enablement for every 'disease or medical condition mediated by a cytokine'," and that the claim does not set forth any steps involved in determining what is "a disease or medical condition mediated by a cytokine." It is respectfully submitted that if the Examiner's justifications for this rejection are correct, *there is no way* that a claim in the format of sample claim 2 could be allowable, even though this format is is *expressly authorized* in the Training Materials. Obviously, this was not the intent of the PTO in promulgating these training materials.

Specifically, sample claim 2 of Training Material Example 8 is directed to a

> "method of treating a disease caused or exacerbated by increased activity of enzyme XYZ consisting of administering an effective amount of compound A to a patient,"

just as present claim 12 is directed toward a

> method for treating a disease or medical condition mediated by the production or effect of a cytokine, said method comprising administering to a warm-blooded animal in need thereof a cytokine inhibiting amount of an amide derivative of the Formula I .

As with enzyme XYZ of sample claim 2, cytokines are well known enzymes carrying out well known reactions. See, *e.g.*, the specification disclsoure beginning at page 1, line 12. Specific disease conditions treatable by the method of claim 12 are also identified in the specification, whereas even a literature disclosure of a specific disease condition treatable by enzyme XYZ was deemed sufficient in sample claim 2.

However, there is no way that every "disease caused or exacerbated by increased activity of enzyme XYZ" could possibly be disclosed or enabled in *any* specification supporting sample claim 2, and there are no "steps" set forth in sample claim 2 by which such disease would be determined. Certainly such requirements could not have been an expectation of the PTO when it approvingly exemplified claims in the format of sample claim 2. Thus, the Examiner's present requirement that claim 12 include such "steps," and that the specification disclose and thus enable treatment of "every disease or medical condition mediated by a cytokine" are unrealistic, and are entirely inconsistent with the PTO exemplification that this format of method claim is acceptable. Therefore, withdrawal of the section 112 rejections of claim 12 is respectfully requested.

Claim Rejections – 35 USC § 112 – other bases

Claim 2 is rejected under section 112, second paragraph, as being indefinite with respect to the limitation "Q is furyl . . ." because of a lack of antecedent basis in claim 1. Similarly, claim 8 is rejected under section 112, second paragraph, as being indefinite with respect to eight and ninth listed compounds, also for lack of antecedent basis. These grounds for rejection have been overcome by the above amendments whereby the recitations noted by the Examiner have been removed. The recitations were inadvertently overlooked when the claims were amended to the scope of the elected invention, and the Examiner is thanked for noting these inconsistencies.

Claim Rejection – 35 USC § 102

Claims 1, 9, 10 and 12 are rejected under section 102 as being anticipated by Ashton (J. Med. Chem). The Examiner specifically points to compound 30 of the reference. The Examiner's attention is respectfully drawn to the fact that this compound 30 is specifically removed from the scope of claim 1 (and claims dependent thereon), by the exclusion at the end of claim 1, specifically the first-named excluded compound, N-(2-cyclohexylethyl)-3-(hydroxybenzamido)-4-methylbenzamide. Therefore, withdrawal of this rejection is believed to be in order, and is respectfully requested.

Acknowledgment of Previously-Cited Documents

The Examiner has initialed and returned with the present action the form PTO-1449 filed herein with the Information Disclosure Statement on August 23, 2001. However, the Examiner has not acknowledged consideration of the documents cited on the form PTO-1449 filed with this application (and dated) February 2, 2001; the form PTO-1449 accompanying the Information Disclosure Statement filed and dated August 20, 2001; or the "related U.S.

Patent Applications cited in the body of the August 20, 2001 Information Disclosure Statement. Copies of the documents and related applications cited in each of these Information Disclosure Statements and/or accompanying forms PTO-1449 were submitted with the respective IDS filings. Consideration of these documents and related applications, and acknowledgement of such consideration by initialing copies of the forms and tables where provided, are respectfully requested.

Conclusion

Claims 2, 3, 5, 6 and 8 have been noted as being allowable if rewritten to overcome the section 112, second paragraph, grounds for rejection and to incorporate the limitations of the base and any intervening claims. However, in view of the above amendments and the foregoing remarks, all grounds for rejection of all claims are believed to have been overcome. Accordingly, withdrawal of these rejections and allowance of all claims are believed to be in order, and are respectfully requested.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: November 6, 2002 By: _____

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APPENDIX
VERSION WITH MARKINGS TO SHOW CHANGES

The following amendments have been made above, wherein deleted material is shown by **[bold text in brackets]** and added material is shown by **bold underlined text**:

IN THE ABSTRACT:

A duplicate abstract (per the Examiner's specific request) has been submitted on a separate page, which is identical to the official abstract that was properly filed in the International Application and submitted with this application as filed.

IN THE TITLE:

The title has bee amended as follows:

[AMIDE] AMIDOBENZAMIDE DERIVATIVES WHICH ARE USEFUL AS CYTOKINE INHIBITORS

IN THE CLAIMS:

Claims 2, 8 and 12 have been amended as follows:

2. (Amended) An amide derivative of the Formula I according to claim 1 wherein R^3 is methyl, ethyl, chloro or bromo;
Q is phenyl which bears 1, 2 or 3 substituents selected from hydroxy, fluoro, chloro, trifluoromethyl, cyano, carboxy, methyl, ethyl, propyl, methoxy, ethoxy, methylenedioxy, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, acetyl, propionyl, chloromethyl, methoxymethyl, methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-chloroethoxy, 3-chloropropoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 3-ethoxypropoxy,

cyanomethoxy, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-acetylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and 3-(4-acetylpiperazin-1-yl)propoxy**[,**

or Q is furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl or naphthyridinyl which optionally bears 1 or 2 substituents selected from hydroxy, fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, methoxy and ethoxy];

p is 0;

q is 0; and

R^4 is phenyl which bears 1 or 2 substituents selected from hydroxy, fluoro, chloro, trifluoromethyl, cyano, amino, methyl, ethyl, methoxy, ethoxy, methylenedioxy, methylamino, ethylamino, dimethylamino, diethylamino, acetyl, propionyl, chloromethyl, methoxymethyl, 2-methoxyethyl, methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-chloroethoxy, 3-chloropropoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 3-ethoxypropoxy, cyanomethoxy, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-aminoethoxy, 3-aminopropoxy,

2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-chloroethylamino, 2-hydroxyethylamino, 2-methoxyethylamino, 2-ethoxyethylamino, 2-aminoethylamino, 2-methylaminoethylamino, 2-ethylaminoethylamino, 2-dimethylaminoethylamino, 2-diethylaminoethylamino, N-(2-chloroethyl)-N-methylamino, N-(2-hydroxyethyl)-N-methylamino, N-(2-methoxyethyl)-N-methylamino, N-(2-ethoxyethyl)-N-methylamino, N-(2-aminoethyl)-N-methylamino, N-(2-methylaminoethyl)-N-methylamino, N-(2-dimethylaminoethyl)-N-methylamino, N-(3-aminopropyl)-N-methylamino, N-(3-methylaminopropyl)-N-methylamino, N-(3-ethylaminopropyl)-N-methylamino, N-(3-dimethylaminopropyl)-N-methylamino, N-(3-diethylaminopropyl)-N-methylamino, phenyl, benzyl, benzyloxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-acetylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and 3-(4-acetylpiperazin-1-yl)propoxy;
or a pharmaceutically-acceptable salt thereof;
except that 3-(2-hydroxy-4-methylbenzamido)-N-(4-hydroxyphenyl)-4-methylbenzamide is excluded.

8. (Twice Amended) An amide derivative of the Formula I according to claim 1 selected from :-
N-(3-dimethylaminophenyl)-4-methyl-3-(4-propylbenzamido)benzamide,
3-(3,4-dimethoxybenzamido)-N-(3-dimethylaminophenyl)-4-methylbenzamide,
3-(4-butoxybenzamido)-N-(3-dimethylaminophenyl)-4-methylbenzamide,

4-chloro-N-(3-dimethylaminophenyl)-3-(4-propylbenzamido)benzamide,
3-(4-carboxybenzamido)-N-(3-dimethylaminophenyl)-4-methylbenzamide,
N-(3,4-dichlorobenzyl)-3-(3,4,5-trimethoxybenzamido)-4-methylbenzamide,
N-(2-cyclohexylethyl)-3-(3,4-dimethoxybenzamido)-4-methylbenzamide,
[N-(3-dimethylaminophenyl)-4-methyl-3-(6-quinolylcarbonylamino)benzamide,
4-chloro-N-(3-dimethylaminophenyl)-3-(6-quinolylcarbonylamino)benzamide,]
4-methyl-N-(3-morpholinophenyl)-3-(3-piperidin-4-yloxybenzamido)benzamide,
4-chloro-N-(3-fluoro-5-morpholinophenyl)-3-[3-(1-methylhomopiperidin-4-yloxy)benzamido]benzamide,
3-(2-diisopropylaminoethoxybenzamido)-4-methyl-N-(3-morpholinophenyl)benzamide,
3-(4-diethylaminomethylbenzamido)-4-methyl-N-(3-morpholinophenyl)benzamide,
4-methyl-3-[3-(4-methylhomopiperazin-1-ylmethyl)benzamido]-N-(3-morpholinophenyl)-benzamide, and
4-methyl-3-[3-(4-methylpiperazin-1-ylmethyl)benzamido]-N-(3-morpholinophenyl)-benzamide;
or a pharmaceutically-acceptable salt thereof.

12. (Amended) A method for treating a disease or medical condition mediated by **the production or effect** of a cytokine, said method comprising administering to a warm-blooded animal in need thereof a **cytokine inhibiting [treatment-effective]** amount of an amide derivative of the Formula I **[as claimed in claim 1]**, or a pharmaceutically-acceptable salt or in-vivo cleavable ester thereof**, according to claim 1**.